

The SNPs Interpretation Guide

By Caledonia (8-24-2014)

Disclaimer: I am not a medical professional, and nothing I say should be considered medical advice, only educational.

This document is meant to work together with the following items, in this order:

1. Methylation Made Easy Video Series
<https://www.youtube.com/watch?v=o4uqEDK6BvM>
2. The SNPs Interpretation Guide
3. Start Low and Go Slow
<http://forums.phoenixrising.me/index.php?threads/start-low-and-go-slow-how-to-be-safe-on-a-methylation-protocol.26711/>
4. Roadblocks to Successful Methylation Treatment
<http://forums.phoenixrising.me/index.php?threads/roadblocks-to-successful-methylation-treatment.29273/>

I assume you've already viewed the Methylation Made Easy video series, which tells you what methylation is, why it's important, the consequences of poor methylation, how folate and B12 interact to create methylation, how a partial methylation block creates the symptoms of ME/CFS, a general approach to treatment, and how to read the SNPs code.

For those unable to view the videos, I've included a section at the end (the Appendix) on how to read the SNPs Code.

Note: Sometimes a gene will be listed as "no call" or "not found". In this case, either 23andme doesn't test for that gene, or there wasn't enough DNA to make a determination of the gene's status.

Part 1 – Interpreting Methylation SNPs

Intro

The first thing is to look for what First Priority mutations you may have. First Priority means to treat these SNPs first before getting into the core methylation SNPs for folate and B12. It doesn't mean that they're any more or less important than the other ones.

First Priority Mutations

ACAT (ACAT1-02) is involved in cholesterol and energy metabolism, helping to mediate the conversion of foodstuffs into biological energy. ACAT dysfunction may lead to B12 deficiency. It regulates the lipid balance and fluidity in cell membranes, impacting neurological function. It mediates the accumulation of oxalates, which, in excess, can cause kidney stones.

SHMT (SHMT1 C1420T) is part of the folate cycle (where MTHFR is). An SHMT mutation often shifts the methylation cycle away from both the long and short routes through the methylation cycle into a side reaction, which is not productive for methylation.

ACAT and **SHMT** – these two are known as the “leaky gut genes”. Presence of these genes may cause a higher incidence of gut problems. If you have gut problems, you will need to treat them with the 4R Gut Rebuilding Program first.

<http://forums.phoenixrising.me/index.php?threads/the-4r-gut-rebuilding-program-summary.25761/>

If you also have ACAT and/or SHMT, treat those at the same time as the gut. This will help your gut program be more successful.

To support ACAT, take ox bile, also called bile salts. Amy Yasko has also designed a supplement called ACAT/BHMT, which would be appropriate if you have both of those SNPs, but it's quite expensive. <http://www.holisticheal.com/acat-bhmt.html>

To support SHMT, take a low dose of folinic acid to help shift methylation activity back to the short and long routes around the cycle. Yasko also suggests using lactoferrin (which helps to control iron levels to regulate SHMT). Heartfixer also suggests methylfolate.

Note that some people do not tolerate folinic acid, and find that it depletes methylfolate and causes methyl trapping symptoms (i.e. feeling worse).

Unfortunately, the new v.4 chip from 23andme no longer has SHMT. In that case, especially if you have gut problems, I suggest taking folinic acid as a precaution (unless, of course, you don't tolerate it). Many methylation protocols and multivitamins contain folinic acid.

CBS (CBS C699T, CBS A360A) is located at the bottom of the methylation cycle, where it leads into the transsulfuration pathway, acting as a gatekeeper. While most SNPs are downregulations (functions slower than normal), CBS is an upregulation (functions faster than normal). With this upregulation, the “gate” is always open, draining any methylation supports you might be taking, causing impaired methylation. This also leads to the creation of harmful byproducts such as excess ammonia and sulfites, instead of glutathione.

There are two SNPs – the major one is **CBS C699T** and the minor one is **CBS A360A**. If you have the major SNP, it's more likely that CBS could cause a problem, than if you just have the minor one.

BHMT mutations will add to CBS problems and can even cause a CBS problem in the absence of CBS SNPs.

So if you have CBS C699T alone, or either CBS + BHMT, or more than one BHMT, it's more likely you could have a CBS problem. If you only have CBS A360A, it's unlikely that could cause a problem (I've only heard of two cases, one of whom is the Heartfixer).

You only have to treat CBS if it's expressed (causing problems). Signs that CBS is expressed are having trouble tolerating sulfur foods or supplements, having trouble tolerating methyl supplements such as methylfolate or methylcobalamin, no matter how small you make the dose. Classic symptoms are a stress/anxiety reaction, similar to a very stressful week at work with deadlines – feeling nervous, butterflies in the stomach, tight painful trapezius muscles and so on. One person on the Phoenix Rising Forum has reported an intense head pressure.

MTHFRsupport also reports that a lot of chronic Lyme cases have CBS. One of the byproducts of Lyme is ammonia, which gets detoxified by the CBS pathway. Lymies who address CBS are seeing a lot of symptom relief from lower back pain and/or neurological problems. This is because they can now handle the ammonia the Lyme is producing.

Besides signs and symptoms, you can also do testing and check for high ammonia and/or a consistently high reading on urine sulfate strips over several days. The "poor man's test" is to just check with the urine sulfate strips. Ammonia is included in the Nutreval test, so you wouldn't have to test for that separately, if you plan on taking this test.

If you have done the HDRI Methylation panel or a similar methylation panel, when the sum of SAM + SAH is below about 268 micromoles per deciliter, that suggests that CBS is expressed.

If you determine that CBS is causing a problem, and you need to do treatment, follow the program outlined on the Heartfixer page.

<http://www.heartfixer.com/AMRI-Nutrigenomics.htm>

I successfully followed this program, except for I didn't take any Yasko RNA's and I used the much easier Free Thiol list instead of the low sulfur diet.

Free Thiol list: <http://www.livingnetwork.co.za/chelationnetwork/food/high-sulfur-sulphur-food-list/>

After you've taken care of your gut, ACAT, SHMT and CBS, you're ready to proceed to the Second Priority Mutations.

Second Priority Mutations

MTHFR (MTHFR C677T, MTHFR A1298C) – Affects the conversion of dietary folate into methylfolate. This will impair methylation, with a wide range of consequences. There are two mutations – **MTHFR C677T**, which is the major one and **MTHFR A1298C**, which is the minor one. To support both types of MTHFR, take methylfolate.

Additionally, to support MTHFR A1298C, after all the methylation cycle supports have been added, BH4 supplementation is also suggested - this mutation depletes BH4 converting methylfolate back to THF (in the folate cycle).

BH4 is necessary to generate neurotransmitters (dopamine, serotonin, and norepinephrine) and nitric oxide, our key vasoprotective molecule, setting you up for neurological, psychological, and cardiovascular disease states.

Having CBS and BHMT in combination with MTHFR A1298C is known as the “BH4 deficiency double whammy”. The toxic metals mercury, lead, and especially aluminum can add to this.

MTR (MTR A2756G)

MTRR (MTRR A66G, MTRR H595Y, MTRR K350A, MTRR R415T, MTRR A664A)

MTR is B12 intake and **MTRR** is B12 recycling. With every spin of the cycle, MTR uses one molecule of B12 to take a methyl group from methylfolate, then tacks it onto homocysteine to form methionine. MTRR regenerates methyl-B12 from available methyl donors and B12. MTR is an upregulation, while MTRR is a downregulation.

Having either of these mutations will impair methylation, causing a wide range of consequences. If you have both MTR and MTRR mutations, this is called the “B12 double whammy”. It will put a worse drain on B12 than having either MTR or MTRR alone.

To support MTR and MTRR, take vitamin B12. There are three active forms of B12 that can be taken – hydroxycobalamin, methylcobalamin and adenosylcobalamin.

To determine the type of B12 to take, look your **COMT V158M** and **VDR taq** combination. Amy Yasko has simplified this on this nifty chart (about halfway down the page). <http://www.scribd.com/doc/132017201/Dr-Amy-s-Simplified-Road-Map-to-Health>

COMT (COMT V158M, COMT H62H) degrades dopamine, norepinephrine, and to a somewhat lesser extent, other neurotransmitter substances by borrowing a methyl group from SAMe. If you are COMT+, dopamine will degrade more slowly, so you will have more methyl groups floating around. If you take methylcobalamin, you risk being overdosed with methyl groups causing mood swings (panic attacks or bi-polar).

Hydroxycobalamin is processed slower so that helps prevent mood swings.

Note - even if the chart says to take hydroxycobalamin, some people don't tolerate it. In that case, you should substitute methylcobalamin (and also take adenosylcobalamin), but be careful not to take too high of a dose, especially when starting.

Note, I have noticed that many people state that they are starting with 1000 to 5000mcg and they don't think they're taking that much B12 – these are high doses, folks! 1 to 100 mcg is a small dose. The same thing applies to methylfolate.

BHMT (BHMT-01, BHMT-02, BHMT-04, BHMT-08) is the secondary “shortcut” methylation pathway. To support this pathway, you can take sunflower lecithin, which converts to TMG. Note that TMG = tri **methyl** glycine, which is another methyl supplement, so take it easy if you're sensitive to methyl supplements.

MAO A (MAO A R297R) breaks down serotonin. A mutation will cause a decreased ability break it down. Defects in serotonin metabolism have been associated with mood and neurological disorders. With +/+ status, serotonin cycling from high to low levels may result in mood swings or even aggressive behaviors. Obsessive compulsive disorder (OCD) behaviors are also a symptom.

Males only have one MAO A mutation, while females have two. Therefore, if you're male, a MAO A + result will be the same as MAO +/+. I believe Genetic Genie is now reporting an MAO A mutation for males as +/+ (highlighted in red) in an effort to make clear what impact it has on functioning.

As MAO requires BH4 for its reaction, lack of BH4 due to aluminum toxicity, increased levels of ammonia, and/or MTHFR A1298C mutations all impact serotonin levels.

For treatment, Yasko suggests getting all the other SNP supports in place first. This should raise BH4 and help to normalize serotonin.

Then if you're still experiencing mental health type issues (anxiety/depression, etc.), supplement with sprinkles (tiny amounts) of 5HTP.

5HTP is a precursor to serotonin, so this is contraindicated if you're also on an SSRI or SNRI anti-depressant type medication. Taking both may cause too much

serotonin in your system, which can cause serotonin syndrome, a potentially life threatening reaction.

VDR Bsm is the Vitamin D Receptor. If you have a mutation, get your Vitamin D tested and if it's low, supplement with D3.

The rest of the methylation SNPs, such as **AHCY**, can be safely ignored as they should become balanced when the other supports are in place.

References:

Heartfixer - <http://www.heartfixer.com/AMRI-Nutrigenomics.htm>

"What IS MTHFR AND Other SNPs That Work With MTHFR" - MTHFRsupport.com
Blog Talk Radio podcast Jan. 31, 2013
<http://www.blogtalkradio.com/mthfrsupport/2013/01/31/what-is-mthfr-and-other-snps-that-work-with-mthfr>

Autism: Pathways to Recovery – Chapter 6 (Amy Yasko)
<http://www.dramyyasko.com/resources/autism-pathways-to-recovery/chapter-6/>

Rich Vank's HDRI Methylation Panel Interpretation -
<http://phoenixrising.me/treating-cfs-chronic-fatigue-syndrome-me/treating-chronic-fatigue-syndrome-mecfs-glutathione-and-the-methylation-cycle/interpretation-of-results-of-the-methylation-pathways-panel-2011>

Part 2 – Interpreting Detox SNPs

Introduction

CYP stands for Cytochrome P240, which is Phase I detoxification.

If you have mutations in a certain pathway you may have trouble with the drugs mentioned and/or you should avoid the toxins mentioned. To get a more extensive list of drugs metabolized by each gene, click on the link below the description and find the "Substrates" list on the drug chart.

In terms of methylation treatment, the most important SNPs are GSTP, GSTT (glutathione) and SOD2 (oxidative stress and mitochondria). The other SNPs can explain why you may have trouble tolerating certain medications, why you may have multiple chemical sensitivities, or how to minimize cancer risk.

The general advice for all detox SNPs is to eat your fruits and veggies, especially cruciferous veggies, and avoid toxins.

Phase I Detox

CYP1A1 (CYP1A1*2C A4889G, CYP1A1 m3 T3205C, CYP1A1 C2453A) – detoxifies polycyclic aromatic hydrocarbons (PAHs) produced from the combustion of organic materials (exhaust fumes, cigarette smoke, charbroiled meats, etc.).

CYP1A2 (CYP1A2 164A>C) – no mutations means a fast caffeine metabolizer, one or two mutations means a slow caffeine metabolizer. Some drugs such as acetaminophen are also metabolized by this pathway, as well as polycyclic aromatic hydrocarbons (PAHs).

<http://en.wikipedia.org/wiki/CYP1A2>

CYP1B1 (CYP1B1 L432V, CYP1B1 N453S, CYP1B1 R48G) – metabolizes estrogen - can cause estrogen dominance, which can cause estrogen related cancers such as breast or uterine cancer in females, and prostate cancer in males. You can eat cruciferous veggies, or take DIM or IC3 (components in cruciferous veggies) to lower estrogen if it's high. Calcium d-glucarate is suggested instead of the DIM or IC3 if you have a CBS or COMT mutation.

CYP2A6 (CYP2A6*2 1799T>A, CYP2A6*20) - detoxifies nitrosamines (beer, cured meats, and dried, smoked or salted fish) and nicotine (tobacco products)

http://en.wikipedia.org/wiki/CYP2A6#CYP2A6_Ligands

CYP2C9 (CYP2C9*2 C430T, CYP2C9*3 A1075C) - detoxifies many substrates such as NSAIDs, Coumadin, glipizide, sulfonylureas, Elavil (amitriptyline), fluoxetine (Prozac), THC (marijuana) and more. If you ever needed to take Coumadin, you would need a lower dose than normal.

<http://en.wikipedia.org/wiki/CYP2C9>

CYP2C19 (CYP2C19*17)- detoxifies proton-pump inhibitors (e.g., Prilosec) and many anticonvulsants (e.g., Valium). Also amitriptyline (Elavil), citalopram (Celexa) and more. <http://en.wikipedia.org/wiki/CYP2C19>

I believe this is an upregulation. I have this mutation and did better with longer acting versions of drugs going through this pathway - so Dexilant instead of Prilosec, and clonazepam (Klonopin) instead of alprazolam (Xanax).

CYP2D6 (CYP2D6 S486T, CYP2D6 100C>T, CYP2D6 2850C>T)- detoxifies ~20-25% of all prescription drugs including tricyclics, MAOIs, SSRIs, opiates, anti-arrhythmics, beta- blockers, Cimetidine, etc.

<http://en.wikipedia.org/wiki/Cyp2d6>

CYP2E1 (CYP2E1*1B 9896C>G, CYP2E1*1B 10023G>A, CYP2E1*4 4768G>A) detoxifies nitrosamines (beer, cured meats, and dried, smoked or salted fish), ethanol (acetaldehyde), and anesthetics.

<http://en.wikipedia.org/wiki/CYP2E1>

CYP3A4 (CYP3A4*1B, CYP3A4*2 S222P, CYP3A4*3 M445T, CYP3A4*16 T185S) detoxifies over 50-60% of all prescription medications, most steroid hormones (cortisol, estrogen, testosterone, etc.) and organophosphate insecticides.

<http://en.wikipedia.org/wiki/Cyp3a4>

Phase II Detoxification

GSTP1 (GSTP1 I105V, GSTP1 A114V) – Glutathione-S-transferase detoxifies many water-soluble environmental toxins, including many solvents, herbicides, fungicides, lipid peroxides, and heavy metals (e.g., mercury, cadmium, and lead). Rich Van Konynenburg hypothesized that glutathione depletion causes the symptoms of ME/CFS.

A mutation means you require more glutathione than the average person. You can raise glutathione indirectly via a methylation protocol. If you decide to supplement glutathione directly, Ben Lynch suggests taking NAD (form of niacin) with it so that you make the good reduced glutathione instead of the bad oxidized glutathione.

GSTT1 - If it's absent, you're missing one of the genes that produce glutathione. This is worse than simply having a mutation. Approximately 15% of the population has this. You may have trouble with xenobiotics (environmental toxins), mercury, etc. Treatment would be to avoid toxins and do methylation treatment and/or other measures to raise glutathione.

GSTM1 affects glutathione. It is not possible to determine if this SNP is present/absent with 23andMe testing.

SOD2 A16V – super oxide dismutase. This affects the mitochondria and thus energy. It can also cause increased oxidative stress (a higher amount of bad oxidized glutathione than good reduced glutathione).

One person with a SOD2 +/- mutation reported that a SOD supplement, Biotec Extra Energy Enzymes got them out of bed. Another person reported this supplement had too much sulfur in it so it wasn't well tolerated.

Another option, suggested by MTHFRsupport, is to supplement with mitochondrial supplements such as carnitine, ribose, Co Q10, NADH, etc. This approach worked better for me than a SOD supplement to increase energy.

Genova Detoxigenomics suggests the following: liberal consumption of dietary antioxidants in colorful vegetables and fruits; broad-spectrum antioxidant supplements may also be helpful, as well as manganese, which serves as a cofactor for SOD2.

NAT (NAT1 R187Q, NAT1 R64W, NAT2 I114T, NAT2 R197Q, NAT2 G286E, NAT2 R64Q, NAT2 K268R) - N-acetyltransferase - detoxifies petrochemicals. People with NAT problems can be chemically sensitive to chemicals like perfume, gasoline, toluene, xylene i.e., multiple chemical sensitivity. Increased risk for developing lung, colon, bladder, or head & neck cancer.

Don't smoke, and avoid second hand smoke and chemicals. Eat your fruits and veggies, especially cruciferous veggies, to help detoxify. Vitamin B5 (pantithene), can help NAT.

References:

Genetic Genie - <http://geneticgenie.org/>

Detoxigenomics Sample Report -
<http://forums.phoenixrising.me/index.php?threads/detoxigenomic-sample-report.30442/>

“What IS MTHFR AND Other SNPs That Work With MTHFR” - MTHFRsupport.com
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“Folate and Methylation Defects and Metabolism in 2013: Clinical Breakthroughs and Updates” by Benjamin Lynch <https://www.youtube.com/watch?v=-lCQp0KkSB4>

Rich Van Konynenburg Glutathione Depletion Hypothesis
<http://phoenixrising.me/research-2/glutathione-depletionmethylation-blockades-in-chronic-fatigue-syndrome/glutathione-depletion-methylation-cycle-block-a-hypothesis-for-the-pathogenesis-of-chronic-fatigue-syndrome-by-richard-a-van-konynenburg-ph-d>

Part 3 – Additional Testing

As the SNPs are just potentials which may or may not be expressed, it can be very beneficial to get some functional testing done to see what’s actually going on in your body.

A good all around test is the **Genova Diagnostics NutrEval test**.
http://www.integrativepsychiatry.net/genova_diagnostics_nutreval.html

When interpreted with the Nutreval Interpretation Guide

<http://forums.phoenixrising.me/index.php?threads/nutreval-interpretation-guide.21468/>

this test can give you a detailed roadmap for treatment. The Nutreval is 5 or 6 tests rolled into one, covering the gut, amino acids, essential fatty acids, neurotransmitters, the Krebs cycle, vitamins, minerals, and detoxification.

Based on the results of the Nutreval, you may decide to do further testing for the gut and/or toxic metals.

The **HDRI Methylation Panel** <http://www.hdri-usa.com/tests/methylation/> is good to get a “before” and “after” picture of your methylation cycle function, but I haven’t found it all that useful for treatment.

The **Doctors Data Methylation Profile**

<http://www.seekinghealth.com/methylation-profile-doctors-data.html> is like a “lite” version of the HDRI Methylation Panel. An interpretation from Ben Lynch may be helpful in getting the maximum information from this test. I’m not sure how useful this test is for treatment.

Appendix

SNPs – Single Nucleotide Polymorphisms

Through genetic testing of genes, we are able to identify the specific genetic mutations, also called “single nucleotide polymorphisms” (or SNPs—pronounced “snips”) within each individual. When the gene is mutated, the protein or enzyme made by the gene is also mutated, thus altering how well it works.

10By identifying the presence of a SNP, we can compensate for it, and give the body the support it needs to perform its tasks successfully.

Understanding the SNPs Code

When you get your SNPs test back, it will appear to be in some sort of secret language. We’ll use MTHFR as an example to explain how to read this code.

The first part of the name of the gene is an acronym for its chemical name. For example, MTHFR stands for methylene tetra hydro **folate** reductase. Notice the word “folate” in its name. This gives you a clue that this gene works on folate, a form of folic acid.

The second part of the name is the SNP. SNPs are spelled out by the numbered position they are on the gene, and by various combinations of the letters G,A,T,C. These letters stand for guanine, adenine, thymine, and cytosine.

The two most common gene mutations or SNPs for the MTHFR gene are C677T and A1298C.

Let's start with C677T.

A normal un-mutated gene is called C677C. This means at the 677th position on the gene, there are two cytosines.

A mutated gene is called C677T. Notice that one of the cytosines has been replaced with a thymine. This one small change is enough to impair it's functioning.

There are two copies of each gene, one from your mother, and one from your father.

If you have one mutated copy, it's written as C677T +/- or heterozygous

If you have two mutated copies, it's written as C677T +/+ or homozygous

The more mutations you have (indicated by the plus signs), the worse your function in that area.

C677T -/- = no loss of function
C677T +/- = 40% loss of function
C677T +/+ = 70% loss of function

The other MTHFR gene mutation is called A1298C.

A normal un-mutated gene is called A1298A.

A mutated gene is called A1298C. Notice that one of the adenines has been replaced by a cytosine. Again, this one small change is enough to impair it's functioning.

If you have one mutated copy, it's written as A1298C +/- or heterozygous
This results in an estimated 10% loss of function.

Two mutated copies
A1298C +/+ or homozygous
This results with an estimated 20% loss of function.

It's also possible to have one mutation on both genes
C677T +/- and A1298C +/- or compound heterozygous

This results in a 50% loss of function.

It's rare, but possible to have 3 mutations, such as C677T +/+ and A1298C +/-.
This results in a 70% loss of function.

It's extremely rare to have 4 mutations. There are only 50 reported cases worldwide.

C677T +/+ and A1298C +/+

This results in an 80% - 100% loss of function

Sadly, these individuals have severe health impairments.

References:

Folate Metabolism and MTHFR: Introductory Overview of an Essential Gene
by Benjamin Lynch, ND, page 17:

<http://www.seekinghealth.com/media/MTHFR-Introduction-Basic.pdf>

Yasko – autism - pathways to recovery -

<http://www.dramyyasko.com/resources/autism-pathways-to-recovery/chapter-6/>

http://en.wikipedia.org/wiki/Methylenetetrahydrofolate_reductase